

AMENDMENT TO THE CLAIMS

▪ **Format of Claim Amendments**

Applicant has amended the claims as indicated below. Pursuant to the revised format to 37 C.F.R. 1.121 adopted by the USPTO in July of 2003, Applicant herein submits only one version of the claims with markings to show changes. A detailed listing of all claims that are, or were in the application, are presented.

**COMPLETE LIST OF CLAIMS THAT ARE OR HAVE BEEN BEFORE THE
OFFICE AFTER ENTRANCE OF THE AMENDMENTS MADE HEREIN (next Page)**

1. (CURRENTLY AMENDED) A method of screening for inhibitors of beta-amyloid production comprising,

- 1) contacting a potential inhibitor of beta-amyloid production and a tagged inhibitor of beta-amyloid production with at least one macromolecule involved in the processing of APP and the production of beta-amyloid peptide, wherein the macromolecule is a secretase selected from ~~alpha~~ α -secretase, β ~~beta~~-secretase, and ~~gamma~~ γ -secretase, said macromolecule containing a binding site specific for said tagged inhibitor of beta-amyloid production;
- 2) separating the tagged inhibitor of beta-amyloid production bound to said macromolecule from the tagged inhibitor of beta-amyloid production free from said macromolecule; and
- 3) determining an inhibitory concentration of the potential inhibitor of beta-amyloid production from the concentration of tagged inhibitor of beta-amyloid production bound to said macromolecule.

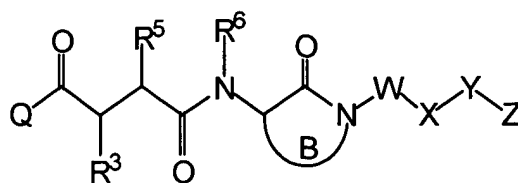
2. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production, a fluorescence labeled inhibitor of beta-amyloid production or a biotin labeled inhibitor of beta-amyloid production.

3. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production.

4. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a tritium or iodine radiolabeled inhibitor of beta-amyloid production.

5. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a tritium radiolabeled inhibitor of beta-amyloid production.

6. (CURRENTLY AMENDED) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (I):



(I)

wherein:

at least one atom of the compound of the Formula (I) is radiolabeled;

Q is NH₂;

R³ is C₁-C₆ alkyl substituted with 0-1 R⁴;

R⁴ is H, OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ carbocycle, C₆-C₁₀ aryl,
or 5 to 10 membered heterocycle;

R⁵ is H, OR¹⁴;

C₁-C₆ alkyl substituted with 0-3 R^{5b};

C₁-C₆ alkoxy substituted with 0-3 R^{5b};

C₂-C₆ alkenyl substituted with 0-3 R^{5b};

C₂-C₆ alkynyl substituted with 0-3 R^{5b};

C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};

C₆-C₁₀ aryl substituted with 0-3 R^{5c}; or

5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5b}, at each occurrence, is independently selected from:

H, C₁-C₆ alkyl, CF₃, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶;

C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};

C₆-C₁₀ aryl substituted with 0-3 R^{5c}; or

5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5c}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl,

F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

R⁶ is H;

C₁-C₆ alkyl substituted with 0-3 R^{6a};

C₃-C₁₀ carbocycle substituted with 0-3 R^{6b}; or

C₆-C₁₀ aryl substituted with 0-3R^{6b};

R^{6a}, at each occurrence, is independently selected from H, C₁-C₆ alkyl, OR¹⁴, Cl, F, Br, I, =O,

CN, NO₂, NR¹⁵R¹⁶, phenyl or CF₃;

R^{6b}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl,

F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

W is -(CR⁸R^{8a})_p-;

p is 0 to 4;

R⁸ and R^{8a}, at each occurrence, are independently selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,

C₂-C₄ alkynyl and C₃-C₈ cycloalkyl;

X is a bond;

C₆-C₁₀ aryl substituted with 0-3 R^{Xb};

C₃-C₁₀ carbocycle substituted with 0-3 R^{Xb}; or

5 to 10 membered heterocycle substituted with 0-3 R^{Xb};

R^{Xb}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl,

F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

Y is a bond or -(CR⁹R^{9a})_t-V-(CR⁹R^{9a})_u-;

t is 0 to 3;

u is 0 to 3;

R⁹ and R^{9a}, at each occurrence, are independently selected from H, C₁-C₆ alkyl or C₃-C₈

cycloalkyl;

V is a bond, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)₂-, -N(R¹⁹)-, -C(=O)NR^{19b}-, -NR^{19b}C(=O)-, -

NR^{19b}S(=O)₂-, -S(=O)₂NR^{19b}-, -NR^{19b}S(=O)-, -S(=O)NR^{19b}-, -C(=O)O-, or -OC(=O)-;

Z is H;

C₁-C₈ alkyl substituted with 0-2 R¹²;

C₂-C₄ alkenyl substituted with 0-2 R¹²;

C₂-C₄ alkynyl substituted with 0-2 R¹²;

C₆-C₁₀ aryl substituted with 0-4 R^{12b};

C₃-C₁₀ carbocycle substituted with 0-4 R^{12b}; or

5 to 10 membered heterocycle substituted with 0-3 R^{12b};

R¹² is aryl substituted with 0-4 R^{12b};

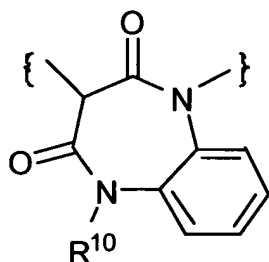
C₃-C₁₀ carbocycle substituted with 0-4 R^{12b}; or

5 to 10 membered heterocycle substituted with 0-3 R^{12b};

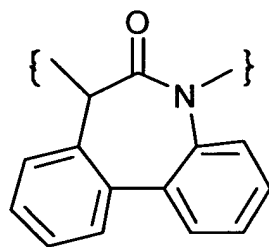
R^{12b}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl,

F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

B is



or



R¹⁰ is H, C(=O)R¹⁷, C(=O)OR¹⁷, C(=O)NR¹⁸R¹⁹,

S(=O)₂NR¹⁸R¹⁹, S(=O)₂R¹⁷;

C₁-C₆ alkyl optionally substituted with R^{10a};

C₆-C₁₀ aryl substituted with 0-4 R^{10b};

C₃-C₁₀ carbocycle substituted with 0-3 R^{10b}; or

5 to 10 membered heterocycle optionally substituted with 0-3 R^{10b};

R^{10a}, at each occurrence, is independently selected from H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl,

OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶, phenyl or CF₃;

R^{10b}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl,

F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

R¹⁴ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;

R¹⁵, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -

C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

R¹⁶, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, benzyl, phenethyl, -

C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

R¹⁷ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;

R¹⁸, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -

C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl); and

R¹⁹, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, phenyl, benzyl,

phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl); and

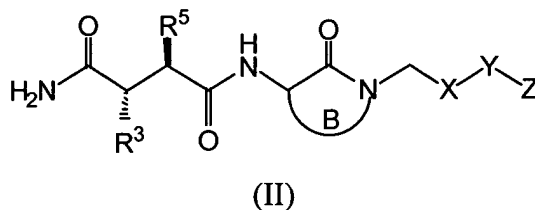
R^{19b} is H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, benzyl or phenethyl; ~~and~~

~~R²⁰ is H or C₁-C₆ alkyl.~~

7. (ORIGINAL) The method of Claim 6 wherein R³ is C₃-C₆ alkyl.

8. (ORIGINAL) The method of Claim 6 wherein R³ is C₃-C₆ alkyl substituted with about 1 to about 4 ³H.

9. (ORIGINAL) The method of Claim 6 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (II):



wherein:

at least one atom of the compound of the Formula (II) is radiolabeled.

10. (ORIGINAL) The method of Claim 9 wherein R³ is C₃-C₆ alkyl substituted with about 1 to about 4 ³H.

11. - 12 (CANCELLED)

13. (CURRENTLY AMENDED) The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and the production of beta-amyloid peptide comprises α ~~alpha~~-, β ~~beta~~- or γ ~~gamma~~-secretase.

14. (CURRENTLY AMENDED) The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and/or the production of beta-amyloid peptide comprises:

- (1) β secretase;
- (2) α secretase; or
- (3) γ secretase;

~~or any fragment or derivative thereof;~~ said macromolecule containing a binding site specific for said tagged inhibitor of beta-amyloid production.

15. (ORIGINAL) The method of Claim 1 wherein the inhibitory concentration is half maximal inhibitory concentration.

16. (PREVIOUSLY PRESENTED) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt form thereof.

17. (CURRENTLY AMENDED) A method for treating ~~degenerative neurological disorders involving similar to~~ Alzheimer's Disease, ~~accumulative beta-amyloid production~~ comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt form thereof.

18. (PREVIOUSLY PRESENTED) A method for treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt form thereof.

19. (CANCELLED)

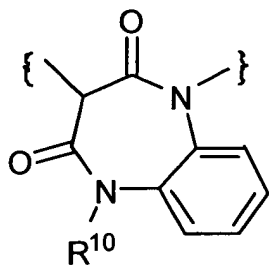
20. (PREVIOUSLY PRESENTED) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production, a fluorescence labeled inhibitor of beta-amyloid production, or a biotin labeled inhibitor of beta-amyloid production.

21. (PREVIOUSLY PRESENTED) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production.

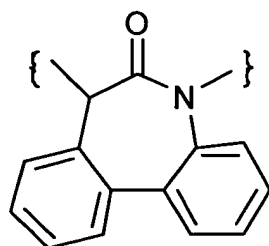
22. (PREVIOUSLY PRESENTED) The method of Claim 1 wherein the tagged inhibitor is radiolabeled with one or more radioisotope selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , and ^{131}I .

23.-35. (CANCELLED)

36. (PREVIOUSLY PRESENTED) An inhibitor of beta-amyloid production comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula as claimed in claim 1 wherein ring B is



or



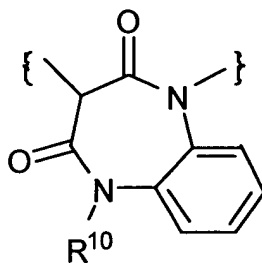
37. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is α ~~alpha~~-secretase, β ~~beta~~-secretase, or γ ~~-secretase~~, ~~or a fragment thereof~~ containing a binding site specific for said tagged inhibitor of beta-amyloid production.

38. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is γ ~~gamma~~-secretase ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

39. (PREVIOUSLY PRESENTED) An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

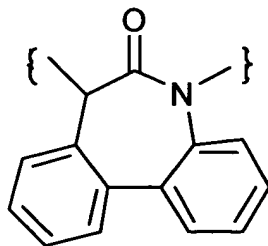
40. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on γ gamma-secretase ~~or a fragment of gamma-secretase~~; wherein the compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

41. (PREVIOUSLY PRESENTED) An inhibitor of beta-amyloid production of Claim 6 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) wherein B is



and the compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

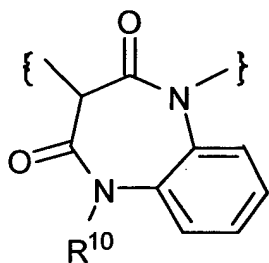
42. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 6 comprising a compound which interacts with a binding site on ~~gamma~~ γ -secretase ~~or a fragment of gamma-secretase~~; wherein said binding site is a specific binding site for a compound of Formula (I) wherein B is



;

and the compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

43. (PREVIOUSLY PRESENTED) A tagged inhibitor of beta-amyloid production of Claim 6 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) wherein ring B is:



or



44. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is α ~~alpha~~-,

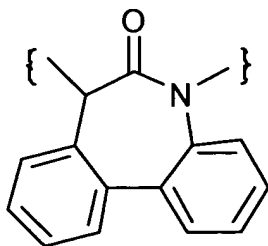
β beta-, or ~~gamma~~ γ -secretase or a fragment thereof, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

45. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is ~~gamma~~-secretase or a fragment thereof, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

46. (PREVIOUSLY PRESENTED) A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

47. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on α alpha-, β beta-, or ~~gamma~~ γ -secretase or a fragment thereof; wherein said tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

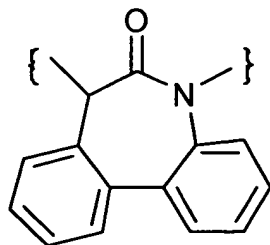
48. (PREVIOUSLY PRESENTED) A tagged inhibitor of beta-amyloid production of Claim 6 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) wherein ring B is



;

and the tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

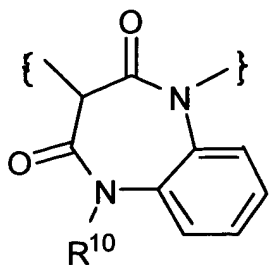
49. (PREVIOUSLY PRESENTED) A tagged inhibitor of beta-amyloid production of Claim 48 comprising a tagged compound which interacts with a binding site on presenilin 1 or a fragment of presenilin 1; wherein said binding site is a specific binding site for a compound of Formula (I) wherein ring B is:



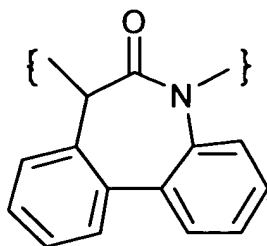
and the tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

50. – 53. (CANCELLED)

54. (PREVIOUSLY PRESENTED) A method of treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production, or a pharmaceutically acceptable salt form thereof, wherein said inhibitor of beta-amyloid production binds to a binding site on a macromolecule involved in the production of beta-amyloid peptide and effects a decrease in production of beta-amyloid peptide;
wherein said binding site is a specific binding site for a compound of Formula (I) of Claim 6 wherein ring B is:

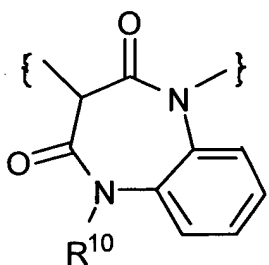


or



55. (CURRENTLY AMENDED) The method of Claim 54 wherein the macromolecule comprises α - secretase, β - secretase, or γ -secretase, ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

56. (PREVIOUSLY PRESENTED) A method of Claim 54 wherein the binding site is a specific binding site for a compound of Formula (I) wherein ring B is:



57. (CURRENTLY AMENDED) The method of Claim 56 wherein the macromolecule comprises α secretase, β secretase, or γ secretase, ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

58. (CURRENTLY AMENDED) The method of Claim 56 wherein the macromolecule comprises γ -secretase, ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

59. (PREVIOUSLY PRESENTED) A method of *in vivo* diagnostic imaging comprising administering to a subject a diagnostically effective amount of a radiolabeled inhibitor of Claim 6 of beta-amyloid production.

60. (ORIGINAL) A method of Claim 59 wherein said method is used in the diagnosis of a neurological disease which involves APP processing or elevated levels of beta-amyloid, or both.

61. (ORIGINAL) A method of Claim 59 wherein said method is used in the diagnosis of Alzheimer's disease.

62. (ORIGINAL) A method of Claim 59 wherein the radiolabeled inhibitor is suitable for imaging of the brain of the subject.

63. (PREVIOUSLY PRESENTED) A method of Claim 59 wherein the radiolabeled inhibitor is radiolabeled with one or more radioisotope selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , and ^{131}I .

64. (CURRENTLY AMENDED) ~~[[A]]~~ The method of Claim 59 wherein the tagged inhibitor of beta-amyloid production is a compound selected from the group ~~any compound~~ found ~~capable~~ of binding a γ ~~gamma~~-secretase ~~or fragment thereof containing~~ at a binding site specific for said tagged inhibitor of beta-amyloid production, ~~such as~~ consisting of 5-amino-6-cyclohexyl-4-hydroxy-hexanamide derivatives, N-aryl amino acid esters, N-heteroaryl amino acid esters, N-arylacetyl amino acid amides, N-heteroarylacetyl amino acid amides, and N-alkylacetyl amino acid amides, N-arylacetyl amino acid esters, N-heteroarylacetyl amino acid esters, and N-alkylacetyl amino acid esters, N-aryl amino acid derivatives, N-heteroaryl amino acid derivatives, and cycloalkyl, lactam, lactone and related compounds.

65. (PREVIOUSLY PRESENTED) A method of Claim 59 wherein the inhibitor of β amyloid production exhibits activity as an inhibitor of γ secretase.

66. - 69. (CANCELLED)

70. (CURRENTLY AMENDED) A method of Claim 59 wherein the inhibitor of beta-amyloid production is selected from:

- (1) an inhibitor of β secretase;
- (2) an inhibitor of α secretase; ~~or~~
and
- (3) an inhibitor of γ secretase.

71. (PREVIOUSLY PRESENTED) A pharmaceutical composition comprising a compound of Claim 6 suitable for in vivo diagnostic imaging comprising a radiolabeled inhibitor of beta-amyloid production.

72. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the composition is used in the diagnosis of a neurological disease which involves APP processing or elevated levels of beta-amyloid, or both.

73. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the composition is used in the diagnosis of Alzheimer's disease.

74. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the radiolabeled inhibitor is suitable for imaging of the brain of the subject.

75. (PREVIOUSLY PRESENTED) A pharmaceutical composition of Claim 71 wherein the radiolabeled inhibitor is radiolabeled with one or more radioisotope selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , and ^{131}I .

76. (CURRENTLY AMENDED) A pharmaceutical composition of Claim 71 wherein the inhibitor of beta-amyloid production is a compound selected from the group ~~any compound~~ found ~~capable of binding a γ secretase, or fragment thereof containing~~ at a binding site specific for said tagged inhibitor of beta-amyloid production, ~~such as~~ consisting of 5-amino-6-cyclohexyl-4-hydroxy-hexanamide derivatives, N-aryl amino acid esters, N-heteroaryl amino acid esters, N-arylacetyl amino acid amides, N-heteroarylacetyl amino acid amides, and N-alkylacetyl amino acid amides, N-arylacetyl amino acid esters, N-heteroarylacetyl amino acid esters, and N-alkylacetyl amino acid esters, N-aryl amino acid derivatives, N-heteroaryl amino acid derivatives, and cycloalkyl, lactam, lactone and related compounds.

77. (PREVIOUSLY PRESENTED) A pharmaceutical composition of Claim 71 wherein the inhibitor of beta-amyloid production is an inhibitor of γ -secretase.